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DEVELOPMENT AND EVALUATION OF COLON SPECIFIC PULSATILE DRUG DELIVERY OF MONTELUKAST SODIUM FOR NOCTURNAL ASTHMA

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ABSTRACT

In the present study, colon specific, pulsatile drug delivery of Montelukast sodium was studied to achieve time and site specific controlled release of Montelukast sodium. The basic design consists of insoluble hard gelatin capsule body filled with microcapsules of Montelukast sodium and sealed with hydrogel plug. The entire Pulsatile device was enteric coated so that the variable gastric emptying can be overcome and a colon specific release can be achieved. The Montelukast sodium micro capsules were prepared and evaluated for FT-IR study, particle size, drug content, in vitro dissolution studies and from the results one better formulation was selected for further design of Pulsatile device. Hydrogel polymers in different concentrations were used as plugs to achieve suitable lag time and it was found that drug release was controlled by the concentration of polymers used. FT-IR and DSC studies showed that there were no interactions between the drug and excipients. In vitro drug release studies of pulsincap dosage forms reveals that the concentration of the polymers used in the plugs and position of plugs determines the lag time thereby affecting the drug release.

KEYWORDS: Colon Specific, Montelukast Sodium, Lag Time & Pulsincap

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Original Article

INTRODUCTION

Among all the controlled drug delivery systems, delivery systems with a pulsatile release pattern are receiving increasing interest for the development of dosage forms. Pulsatile release is meant as the timed liberation of drugs following the programmable lag phases [1]. After lag phase, the drug liberation may be prompt and quantitative, sustained over a prolonged period of time [2-5]. These are designed for chronopharmacotherapy based on circadian rhythm [6]. Pulsatile drug delivery systems may be time specific or site specific. In order to attain a time controlled drug release in to the colon Pulsatile drug delivery systems are basically provided with an outermost enteric film to prevent gastric emptying [7]. To attain the colonic release the lag time should equate to the time taken for the system to reach colon. The systemic absorption from the colon can also be used as means of achieving chronotherapy of diseases that are sensitive to circadian rhythm such as asthma, angina and arthritis [8]. Targeting drug to the colon is also useful when delay in absorption is desired from a therapeutic point of view, such as treatment of disease that have peak symptomsearly in the morning like nocturnal asthma, angina and arthritis[9]. Diseases requiring pulsatile drug delivery systems include Asthma, peptic ulcers, CVS disorders arthritis and

Hypercholesteremia. These diseases display acute symptoms in the early morning [10]. In nocturnal asthma, the airway resistance increases progressively at night and circadian changes are seen in normal lung function. Lung function is usually highest at 4 PM. and lowest at 4 AM where asthma symptoms are prevalent [11].

Janugade B. U. *et al* [12] has developed a press coated tablet of Montelukast sodium by using microcrystalline cellulose, Cross carmellose sodium, as inner core and Ethyl cellulose, L-HPC as an outer layer. The main drawback of the press coated technique is, Multiparticulate systems cannot be delivered by using the press coated technique. Hence capsules were selected as alternative cores to deliver the multiparticulates. Since, pulsincap technique has not developed for Montelukast sodium, hence in the present study an attempt was made to develop colon specific, pulsincap dosage forms for Montelukast sodium which can deliver the drug at the required time. Pulsincap is a novel drug delivery system which can release its drug contents in required time at specific sites in the GI tract. Modified pulsincap consists of non-disintegrating body and a soluble cap filled with their drug formulation and plugged with a swellable hydrogel at the open end. Upon contact with dissolution media or gastrointestinal fluid, the plug swells and comes out of the capsule after a lag time. The lag time prior to the drug release can be controlled by the dimension and position of the plug [13]. Montelukast sodium is an anti- asthmatic drug which requires night time dosing having a biological half-life of 2.2-5.5 hours with good intestinal absorption which makes it an ideal candidate for the chrono pharmaceutical drug delivery system.

MATERIALS AND METHODS

Montelukast sodium was received as a gift sample from Rachem, Hyderabad. Eudragit L 100 was obtained from strides Orco labs, Banglore, sodium alginate, HPMC, Xanthan gum, Guar gum was procured from SD Fine Chemicals, Mumbai. All other chemicals used and received were of analytical grade.

METHOD

Preparation of Microcapsules

The method preferred is an ionic gelation technique [14]. The method involves weighing the specified quantity of sodium alginate and dissolving it in sufficient quantity of distilled water to form a homogeneous polymer solution, and then specified quantity of Eudragit L 100 was added to it and uniformly mixed with the help of magnetic stirrer. Core material, i. e. Montelukast sodium was dispersed in it and mixed thoroughly to form a smooth viscous dispersion, this dispersion was then added drop wise by using needle in 100 ml of 5% $Cacl_2$ solution under continuous stirring at 200 rpm. Stirring was continued for 30 min to make dispersion fine. Then formed microcapsules were filtered and dried at room temperature. The microcapsules were then stored in a desiccator over fused calcium chloride. Five batches were prepared with different proportions of core to coat materials (Drug :Na alginate; Eudragit L100=0.05:1:0.2, 0.05:1:0.4, 0.05:1:0.6,0.05:1:0.8,0.05:1:1(w/w) named F1-F5 respectively). Particle size of different formulations was illustrated in (Table 1).

Preparation of Cross Linked Gelatin Capsules [15, 16]

25 ml of 15 % formaldehyde solution was taken in to a desiccator and to this a pinch of potassium permanganate was added to generate formalin vapors. The wire mesh containing the empty bodies of 250 mg capacity hard gelatin capsules was then exposed to formaldehyde vapors. The desiccator was tightly closed and sealed. The reaction was carried out for 12 hrs and then these empty bodies were removed and kept on a filter paper and dried for 48hrs to ensure complete reaction between gelatin and formaldehyde vapors, afterwards the bodies were kept in an open atmosphere, to facilitate

removal of residual formaldehyde. Then these capsule bodies were capped with untreated cap and stored in polythene bag.

Formulation of Pulsincap Drug Delivery System [17,18,19]

The microcapsules equivalent to 10 mg of Montelukast sodium were incorporated into the treated bodies of empty capsule shells by hand filling and plugged with HPMC, Xanthan gum, and Guar gum polymers as plugs (P1, P2, P3, P4, P5, P6). (Table 2). The cap and body were joined by using 5% Ethyl cellulosic ethanolic solution. Then these capsules were coated with 5 %CAP solution (Cellulose Acetate Phthalate) composed of 8: 2 (v/v) of acetone and ethanol as a solvent with dibutyl phthalate as plasticizer. Coating was repeated until 8-12 % wt. gain was observed. The coating was done to prevent variable gastric emptying. The formulation was shown in Table 3.

Drug Excipient Interaction Study

Drug excipient interactions were determined by using FT-IR studies and DSC studies. FT-IR studies were performed using FT-IR Spectrophotometer (BRUKER ALPHA E) using the OPUS software. The FT IR studies were carried on Montelukast sodium, Montelukast sodium microcapsules and blank microcapsules. DSC studies were performed by using METTLER TOLEDO 822E equipment using E star software in temperature ranging of 25-250º at a heating of 10ºC/min with a stream of nitrogen. DSC studies were carried on Montelukast sodium and Montelukast with excipients.

EVALUATION

Particle Size and External Morphology

The average particle size of the microcapsules was determined by using optical microscopy. External morphology of microcapsules was determined by Scanning electron microscopy (SEM). SEM studies were carried out by using CARLZEIS, EVOMA-15 instrument with 20 kv power.

Micromeritic Properties [20,21,22, 23]

The flow properties of microcapsules were determined by compressibility index and Angle of repose. Angle of repose was performed using the funnel method. A funnel with the end of stem cut perpendicular to the axis of symmetry is secured with its tip at a given height (2cm) H, above graph paper was placed on a flat horizontal surface. The microcapsules were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. Thus R being the radius of the base of the microcapsules conical pile. Results of micromeritic properties of microcapsules were shown in Table 4.

θ =$\tan^{-1}$ h/r.

Where θ is the angle of repose.

Compressibility index was determined by using the formula

$$Compressibilityindex = \frac{Tappeddensity - Bulkdensity}{Tappeddensity}$$

Practical Yield

Practical yield was calculated as the weight of microcapsules recovered from each batch in relation the sum of the material. The percentage yield of Montelukast sodium in the microencapsulated product is determined by using the formula.

$$\%yield = \frac{weightofmicrocapsules}{theoroticalweightofdrugandpolymer} \times 100$$

Drug Content

In a 100 ml volumetric flask, 10 mg of crushed microcapsules was taken, and volume was made up to mark with water+ SLS. The flask was shaken for and then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 345.8nm using UV absorption spectroscopy. Results were shown in Table 5.

%drug content was calculated for all batches using the equation as follows.

$$\%drugcontent = \frac{actualdrugcontentofmicrocapsules}{theoroticalweightofdruginmicrocapsules} \times 100$$

$$\%encapsulationefficiency = \frac{\%drugcontent}{\%\ theoroticaldrugcontent} \times 100$$

***Invitro* Release Studies**

Invitro dissolution profile of each formulation was determined by employing USP Dissolution Apparatus II (900ml of water +SLS, 50 rpm, 37±0.5℃. Microcapsules equivalent to 10 mg of Montelukast sodium were taken and added to dissolution medium.5ml of the sample was withdrawn from the dissolution medium at suitable time intervals and the same amount was replaced with fresh dissolution medium. The absorbance of the filtrate was determined at a wavelength of 345.8 nm by using UV Visible spectrophotometer against water +SLS as blank. The amount of the drug present in the filtrate was then determined from the calibration curve and cumulative % drug release was calculated. From the results the optimized formulation was determined. All the tests were performed in triplicate.

Evaluation of Pulsincap Dosage Forms

Weight Variation

20 capsules were selected randomly from each batch and weighed individually for weight variation. The test requirements are met if none of the individual weights are less than or more than 110% of the average.

Solubility Studies of Treated Capsules

The solubility test was carried out for normal capsules and formaldehyde treated capsules for 24 hrs. Ten capsules were randomly selected and then subjected to solubility studies at room temperatures in dissolution medium and stirred for 24 hrs. The time at which the capsule dissolves or forms a soft, fluffy mass was noted. When the capsules were subjected to solubility studies in different buffers for 24 hours, the following observations were made in all the cases normal capsules, both cap and body dissolved within 15minutes. In the cases of formaldehyde treated capsules, only the cap dissolved within 15 min, while the capsule remained intact for about 24 hrs. The results were shown in Table 6.

Swelling Index

The prepared plugs were weighed and transferred into a petriplate. The initial weight of each plug was determined. 20ml of the dissolution medium (water+SLS) was poured in to the petriplate and each plug was kept in the petriplate and kept aside for 6hrs. The weight of each plug at specified time intervals was noted. Swelling index was calculated using the formula

$$Swellingindex = \frac{Wt-Wo}{Wt} \times 100$$

Wt.= Final weight of the plug at time‘t’

W_0=Initial weight of the plug

The results were illustrated in Table 7.

***Invitro* Dissolution Studies**

Invitro dissolution studies of pulsincap dosage forms were performed using 0.1 N Hcl as dissolution medium for the 1st 2 hrs, (Since the average gastric emptying time is 2 hrs.) and in 5% w/v aqueous solution of sodium lauryl sulfate for subsequent hrs. The dissolution medium was maintained at a temperature of 37±0.5℃, the speed rotation of the paddle was maintained at 50 rpm. The capsules were tied to a cotton thread to prevent floating.5ml of the samples were manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh 5% w/v aqueous solution of sodium lauryl sulfate solution maintained at the same temperature. The samples were analysed at 345.8nm using a UV spectrophotometer. The lag time and percentage release were determined of each formulation. All the tests were conducted in triplicates.

Stability Studies

After determining *invitro* dissolution studies, the optimized formulations (F6, F8. F10) were subjected to Accelerated stability studies (40℃±2℃/75%RH ±5%RH) as per ICH guidelines. The pulsincap dosage forms were packed in HDPE container and kept in stability chamber. The samples were determined for drug content, *invitro* dissolution studies after storage.

RESULTS AND DISCUSSIONS

From the spectra of pure drug and the pure drug with excipients, it was observed that all characteristic peaks of pure drug were present in the combined spectrum, thus indicating compatibility of the drug and polymer. (Figure 1, 2). From the DSC thermo grams of pure drug and the pure drug with excipients the melting point of Montelukast sodium was not changed to indicate the compatibility of drugs with excipients (Figure 3, 4.) Different formulations of microcapsules of Montelukast sodium were prepared by the ionic deletion method. The particle size of the microcapsules was determined by using optical microscopy. (Table 1, Figure 5). Microcapsules were studied for Micromeritic properties, Practical yield, Drug content, Entrapment efficiency, *and invitro* dissolution studies. The results of bulk density and Tapped density were ranged from 0.21±0.036 to 0.242±0.087, 0.238±0.048 to 0.263±0.067 respectively. The results of Angle of repose, Compressibility index, and Hausner’s ratio ranged from 10.20±0.059 to 27.2±0.021, 3.78±0.065 to 11.76±0.058, and 1.038±0.015 to 1.13±0.049. The results of angle of repose (<30) indicates good flow property of microcapsules. This was further confirmed by, lower compressibility index, values and lower Hausner’s ratio (Table 4). The results of the Practical yield were ranges from 84 to 97 %. The results of the Drug content were ranged from 90.07±0.0264 to 98.49±0.124 %. The entrapment efficiency results were ranged from 82.45 to 97.56 (Table 4). The *invitro* release results of F1, F2, F3, F4, and F5 were 99.61±0.346, 99.31±0.2, 98.744±0.44, 99.31±0.403, and 81.57±0.127 respectively. The F4 formulation showed 99.31±0.403 at the end of 7hrs. Hence F4 was selected for designing of pulsincap. The results of the dissolution studies of F1, F2, F3, F4, and F5 formulations indicated that the drug release was decreased with increasing concentration of Eudragit L100. This may be due to increased viscosity of Eudragit L 100. (Fig 6). The release of Montelukast sodium from all the microcapsules formulation followed Zero order, because the r^2 value of Zero order was found to be greater than the r^2 value

of the first order. The r^2 value of the Hixson Crowell plot was found to be greater than the r^2 value of Higuchi plot. Hence the mechanism of drug release is Dissolution controlled. From all the results F4 was found to be the best formulation (Table 8). The solubility of untreated hard gelatin capsules and formaldehyde treated hard gelatin capsules was determined(Table 6). This F4 formulation was filled in to the hard gelatin capsules and the plugs (P1, P2, P3, P4, P5 and P6) are plugged in the capsules. The lag time of the different plugs in different concentrations were determined (Table 2). The degree of swelling of plugs was determined (Table 7). The average percentage deviation of all the prepared pulsincaps was found to be within the pharmacopoeial limits (Table 3). *Invitro* release profiles of pulsatile device for 12 hours studies were found to show good sustaining capacity. During dissolution studies, it was observed that, the enteric coat of the CAP was intact for 2hrs in 0.1N Hcl. In water +SLS the cap of the capsule was dissolved, and the polymer plug was exposed to the dissolution medium, and it absorbs the surrounding fluid, swelled and released the drug through swollen matrix. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body, and then releases the microcapsules in to the dissolution medium (water+SLS). With all the formulations, there was absolutely no drug release in 0.1N Hcl, thus indicating the efficiency of 5% CAP for enteric coating. With formulations F6, F7 at the end of 12^{th} hour drug release was 99.31%, 90.43 % respectively. With formulations F8, F9 at the end of 12^{th} hour drug release was 99.45%, 91.77% respectively. With formulations F10, F11 at the end of 12^{th} hour drug release was 99.13%, 67.41% respectively (Figure 7). The release of Montelukast sodium from the microcapsules in the pulsincap dosage form followed Zero order because the r^2 value of Zero order kinetics was found to be greater than the r^2 value of First order kinetics. Hence the drug release follows zero order kinetics. As the r^2value of the Hixson Crowell plot was found to be greater than the r^2 value of Higuchi plot it can be concluded that the mechanism of drug release follows Dissolution mechanism (Table 9). The results of the accelerated stability studies reveals that there is no change in physical appearance and stickiness of Pulsincaps during storage and observed no significant variation in *in vitro* dissolution studies before and after storage.

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APPENDIES

Table 1: Particle Size of Different Formulations

S. no	Formulation Code	Particle Size(µm)
1	F1	113
2	F2	128
3	F3	156
4	F4	100
5	F5	189

Table 2: Formulation of Plugs

Code	Polymer	Quantity(mg)	Lactose	Total(mg)	Lag Time(hrs)
P1	HPMC	70	30	100	6
P2		50	50	100	5
P3	Xanthangum	60	40	100	6.5
P4		30	70	100	5
P5	Guar gum	30	70	100	7
P6		10	90	100	5

Table 3: Formulation of Pulsincap Dosage Forms

Code	Wt. of Empty Capsule (g)	Wt. of Microcapsules (g)	Polymer Used	Wt. of Polymer (mg)	Wt. of Capsule before Coating(g)	Wt. of Capsule after Coating(g)	Wt. Variation (%) ±SD*
F6	0.25	0.24	HPMC E5	50	0.36	0.39	2.564±0.51
F7	0.25	0.24	HPMC E5	70	0.35	0.38	2.55±0.36
F8	0.25	0.24	Xanthan gum	30	0.32	0.35	2.64±0.258
F9	0.25	0.24	Xanthan gum	60	0.31	0.36	2.52±0.47
F10	0.25	0.24	Guar gum	10	0.30	0.34	2.52±0.85
F11	0.25	0.24	Guar gum	30	0.29	0.33	2.53±0.51

***represents average value±SD* (n=20).**

Table 4: Evaluation of Micromeritic Properties of Microcapsules

Formulation Code	Bulk Density(g/ml)	Tapped Density(g/ml)	Compressibility Index(%)	Hausner's Ratio	Angle of Repose(θ)
F1	0.21	0.238	11.76	1.13	19.2
F2	0.242	0.263	8.67	1.086	13.32
F3	0.228	0.242	5.78	1.061	10.20
F4	0.225	0.254	11.41	1.128	27.2
F5	0.234	0.243	3.70	1.038	16.69

Table 5: Evaluation Studies of Microcapsules

Formulation	%Yield	Drug Content (%)±SD*	Entrapment Efficiency (%)±SD*
F1	84	90.07±0.0264	89.74±1.89
F2	92	92.46±0.02	90.92±1.54
F3	95	91.67±0.026	85.86±1.45
F4	97	98.49±0.124	97.56±1.23
F5	94	92.14±0.120	82.45±1.55

*** represents average value ±SD (n=3)**

Table 6: Solubility Studies of Hard Gelatin Capsules

	Cap	Body
Treated capsules	15min	24hrs
Untreated capsules	15min	15min

Table 7: Swelling Studies of Plugs

Time(hrs)	Degree of Swelling (%)		
	HPMC	Xanthan gum	Guargum
0	0	0	0
2	33.3	47.36	52.38
4	50	60	62.12
6	61.5	66.6	70.58

Table 8: Correlation Coefficient Values in the Analysis of Release Data of Montelukast Sodium Microcapsules as Per Various Kinetic Models

Formulation Code	Zero Order (R^2)	First Order(R^2)	Higuchi Value(R^2)	Hixson Crowell Cube Root Value(R^2)
F1	0.826	0.693	0.874	0.911
F2	0.906	0.689	0.785	0.955
F3	0.905	0.727	0.815	0.955
F4	0.928	0.657	0.844	0.906
F5	0.955	0.776	0.906	0.932

Table 9: Correlation Coefficient (R^2) Values in the Analysis of Release Data of Pulsincap Dosage Forms of Montelukast Sodium as Per Various Kinetic Models

S. No	Formulation Code	Zero Order Kinetics(r^2)	First Order Kinetics(r^2)	Higuchi Kinetics(r^2)	Hixson Crowell Cubic Root Kinetics(r^2)
1	F6	0.9002	0.6583	0.7028	0.792
2	F7	0.8828	0.7815	0.636	0.809
3	F8	0.9185	0.6689	0.7121	0.804
4	F9	0.7836	0.7505	0.5969	0.7559
5	F10	0.8967	0.8735	0.7223	0.8353
6	F11	0.7061	0.711	0.5011	0.6921

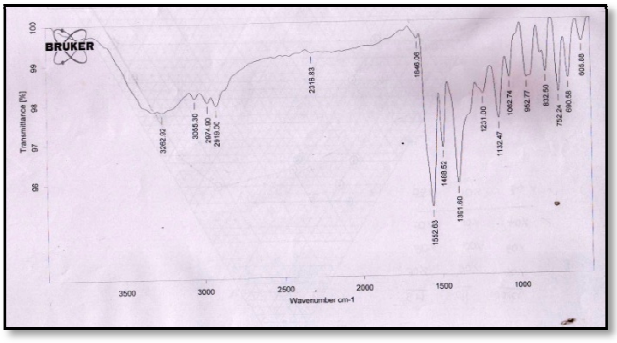

Figure 1: ATR Spectrum of Pure Montelukast Sodium

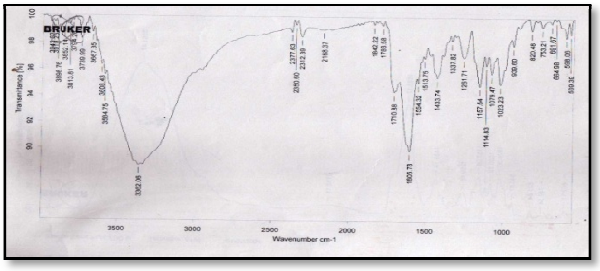

Figure 2: ATR Spectrum of Pure Drug with Excipients

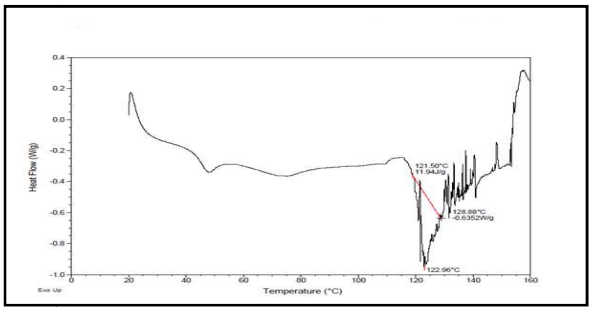

Figure 3: DSC Thermogram of Montelukast Sodium

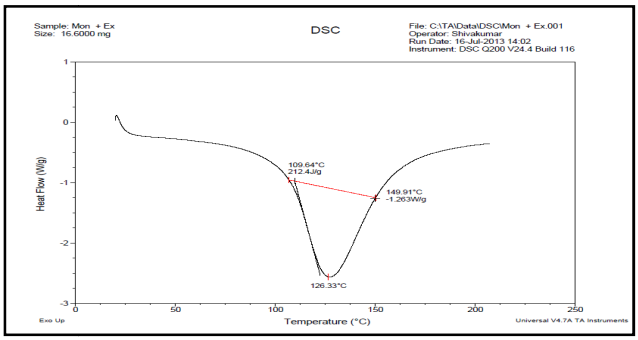

Figure 4: DSC Thermogram of API and Excipients

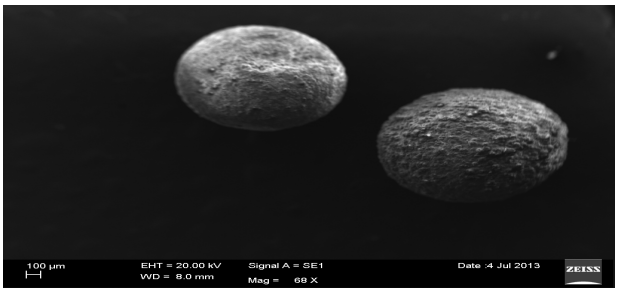

Figure 5: SEM Photograph of Optimized Formulation (F4)

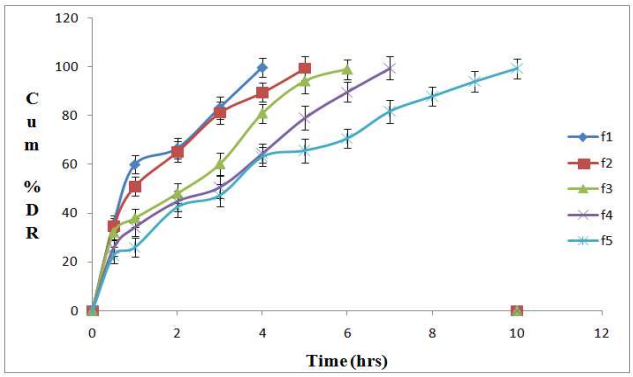

Figure 6: Release Profiles of Different Formulations of Montelukast Sodium Microcapsules

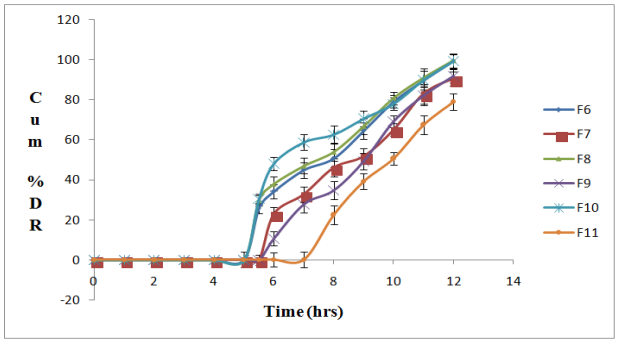

Figure 7: Release Profiles of Different Formulations of Montelukast Sodium Pulsincap Dosage Forms